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Book Review

GENETIC VARIATION AND HUMAN DISEASE: PRINCIPLES AND EVOLUTIONARY APPROACHES
Kenneth M. Weiss
Published by Cambridge University Press, Cambridge, New York, and Melbourne, 1993
354 pp.

There seems to be a continuing intellectual tension between the principal approaches to science: reduction and synthesis. Although there are strong voices on each side, both approaches are necessary in order to achieve reasonable understanding. This is a textbook that will benefit future workers in a number of areas: those working at the bench in molecular biology or biochemistry, the field worker in ecology or anthropology, the clinician, population geneticist, demographer, public health worker, or policy maker.

It is refreshing to read a textbook that does not attempt to treat each topic exhaustively, but rather chooses to highlight the essentials so the reader really is able to concentrate on the principles rather than the minutiae and has a context in which new ideas may be understood. Limitations of knowledge are recognized. The context for this work is the evolution of human phenotypes, with an emphasis on those complex characteristics that produce the prevailing disorders of an adult population rather than the rare disorders, although the latter are included. This also reflects the research contributions of the author.

Using human examples, the chapters of the first two parts provide the background in molecular and population genetics essential to the discussion of evolution and the understanding of disease that Weiss develops, namely, human disorders are an essential part of our basic biologic structure. In conformity with present usage, population genetics is now called genetic epidemiology and also includes analyses of threshold or continuous characteristics as well as dichotomous traits. There is an appropriate emphasis on linkage analysis, since this is the bridge between classical genetics and molecular technology. The approach is largely statistical, but without bogging down in the complex, underlying mathematics. I have frequently thought that this kind of thinking would be helpful to residents and medical students in formulating and understanding the process of differential diagnosis in the purely clinical setting, but have expected it would produce a great deal of resistance.

Part III is the central discussion. Human diseases are placed in the context of mutation rates, selection, genetic drift, and evolutionary history. Well-studied systems are summarized, such as the structure of hemoglobin, the thalassemias, cystic fibrosis, and Tay-Sachs disease. Extensions to quantitative traits are well presented, including diabetes mellitus, hyperlipidemia, and hypertension.

A further integration of genetics and the environment appears in part IV, including revisiting lipid metabolism and hypertension, but also discussing the immune system and human leukocyte antigens and the interrelations with infectious disease. Nonmendelian contributions to variation, such as chromosomal nondisjunction, meiotic drive, somatic mosaicism, and imprinting are presented. The last subject chapter illustrates concepts in the genetics of cancer and aging. Both somatic and nuclear genes are discussed, along with the multistep nature of the pathogenic process.

The afterword reiterates the conceptual framework of the book. There is an important warning: "The inevitable rush of enthusiasm to screen samples, families, or populations for causal alleles for every type of trait will produce many irreproducible results and excessive claims. I think we will be forced to accept that we cannot understand a trait well by enumerating all of its individual 'causes,' which will be quixotically ephemeral and environmentally plastic. Instead, we need to identify deeper structures that can reduce the dimensionality of variation and explain it in a simpler way." The reader needs to keep in mind that these are complex, often chaotic systems. The clue to the underlying order, for Weiss, is evolutionary history. There is a relationship between the genotype and the phenotype, however, selection acts on the phenotype which has environmental components. He remains true to his own evolution as part of the Neel-Schull school of human genetics.

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